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Regular Article

Interfacially-mediated oxygen inhibition for precise and continuous poly (ethylene glycol) diacrylate (PEGDA) particle fabrication

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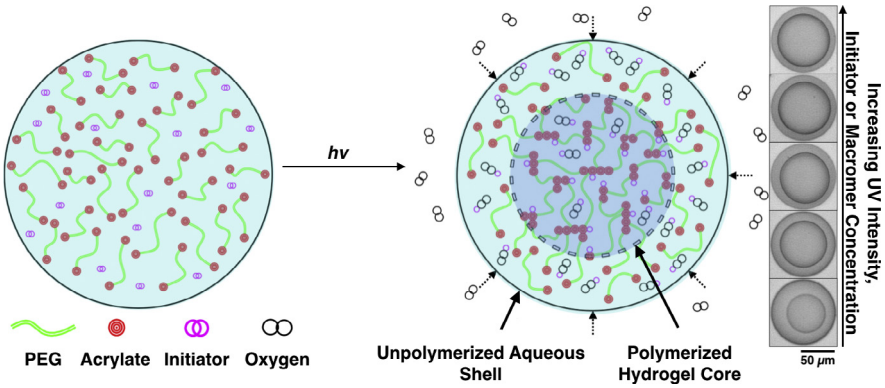
GRAPHICAL ABSTRACT



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ABSTRACT

Hydrogels based on poly(ethylene glycol) diacrylate (PEGDA) have been engineered for a variety of biomedical applications including drug delivery, cell delivery, and tissue engineering. The miniaturization of these materials to nanoscale and microscale particles has been a subject of intense activity, and promises to extend their range of applicability. In general, however, these efforts have been frustrated by the inhibition of chain growth polymerization by oxygen, an effect that is exacerbated as target length scales are reduced. Here, we report a method that exploits the undesirable oxygen-inhibited photopolymerization to produce size-controlled PEGDA hydrogel particles. The role of initial solution composition in determining the relative particle to droplet size ratio is reported, and is found to contribute through its influence on the polymerization rate, as well as the diffusivity of oxygen. Facile control of photopolymerization kinetics via UV light intensity and/or exposure time, allowed PEGDA particles to be produced with dimensions independent of the parent spherical droplets formed by conventional microfluidic emulsification.

1. Introduction

Biomaterials, such as polymers [1], ceramics [2], and metals [3] are widely used in biomedical diagnostic, therapeutic, and prosthetic applications. Among these, hydrogels, defined as water-swollen, crosslinked hydrophilic polymer gels, have shown great potential for biological and medical applications [4]. Synthetic hydrogels have become a focus of particular interest in the last twenty years due to their well-defined structure that can be modified to add functionality and programmed degradability [5]. In particular, hydrogels of poly(ethylene glycol) diacrylate (PEGDA)

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have been investigated for tissue engineering [6,7] and drug delivery [8–11] applications because of their biocompatibility, non-immunogenicity, resistance to protein adsorption, and adjustable mechanical properties and chemical composition [12,13]. Functional hydrogels can be tailored to possess well-defined permeability and stiffness [14], to be sensitive to temperature [15], and to degrade hydrolytically [16,17], photolytically [18,19], or enzymatically [20]. Among the advantages of PEGDA, its ability to be photopolymerized is most notable, as it lends spatial and temporal control over hydrogel properties [21], adding to its versatility and convenience [22].

Hydrogels are typically formulated as bulk structures, such as films and monolithic molds, but emerging applications demand miniaturization for delivery and transport in microscopic environments [23]. In comparison to traditional polymeric nanocarriers such as micelles, liposomes, and polymerosomes, hydrogel particles in the micron and submicron size range offer many advantages, such as controlled loading, versatility in material composition and type of biological cargo, and physical stability [24]. These particles have been previously synthesized by bulk emulsion and dispersion polymerization, which result in a highly polydisperse particle size distribution [25]. More recently, droplet microfluidic particle templating has gained popularity due to its accurate control over particle size and dispersity [26]. Droplet-based microfluidic systems utilize two flowing immiscible phases, usually in combination with a stabilizing surfactant, to form discrete droplets at a channel junction via interfacial instabilities [27]. The size of formed droplets depends upon viscous forces, interfacial chemistry, and channel geometry. However, while droplets in the 10–60 μm range have been reliably produced [28], production of droplets with diameters <10 μm or even submicron is still challenging due to the high shear energy required to overcome the interfacial forces in aqueous solutions.

Microfluidic methods such as tipstreaming in a flow focusing device [29,30], electrospraying [31], satellite droplet collection [32], and droplet shrinking [33,34] have been used to obtain submicron droplets. However, these methods all possess shortcomings that constrain their utility. Tipstreaming, for instance, requires a high viscosity ratio between the immiscible phases and high surfactant concentrations. As a result, it is very sensitive to pressure fluctuations, and fails when using aqueous solutions with high macromer concentrations due to viscoelastic memory effects. Electrospraying requires high energy input and very high flow rate ratios, and is dependent upon the conductivity of the liquids used. Moreover, none of these methods have been coupled with *in situ* photopolymerization to continually produce hydrogel particles, resulting in decreased monodispersity as a consequence of random droplet coalescence during the collection process.

Photopolymerization of PEGDA droplets in microfluidic devices has experienced limited adoption due to challenges arising primarily from oxygen inhibition effects. The inhibition of PEGDA photopolymerization occurs as a result of the rapid reaction of oxygen with photoinitiator and propagating monomer radicals to form peroxides, resulting in no or incomplete polymerization where oxygen is present in surplus [35–38]. All acrylates are inherently vulnerable to oxygen inhibition, and thus, dissolved oxygen must be almost completely consumed before the polymerization reaction can occur. In the case of PEGDA, the consumption of oxygen results in an induction period before which no PEG macromer is converted to crosslinked hydrogel [39]. At oxygen rich interfaces, a competition occurs between the photopolymerization reaction and oxygen diffusion due to the replenishment of oxygen. This is particularly relevant to the photopolymerization of thin films [40] and within gas permeable polydimethylsiloxane (PDMS) microfluidic devices [41,42]. Attempts to counteract the effects of oxygen inhibition include oxygen scavengers, reducing agents, potent photoinitiators, and purging with an inert gas [43,44]. It is possible to photopolymerize emulsion droplets flowing within PDMS microfluidic channels by implementing one or more of these methods, but they either increase the complexity of the microfluidic device design or require adding reactive chemical species into the system, which is generally undesirable for biomaterials applications.

While oxygen inhibition is generally regarded as undesirable, stop flow lithography [45] and gradient-mediated photopatterning techniques [46] have exploited the presence of oxygen in microfluidic devices to obtain uniquely shaped particles. In droplet microfluidics, the oxygen inhibition effect can be observed at the interface between aqueous droplets and the surrounding oil. This effect is pronounced when using oils with high oxygen solubility and diffusivity, as they provide a constant flux of oxygen to the droplets. Upon UV exposure, spherical hydrogel particles are polymerized at the droplet center and are surrounded by an unpolymerized shell, the thickness of which has been shown to be independent of the total droplet diameter [47]. This behavior, arising from equal rates of oxygen reaction and diffusion, presents a unique platform to obtain hydrogel particles with smaller diameters than that of the droplet. Fig. 1 schematically describes droplet photopolymerization in a microfluidic channel with oxygen present and illustrates how a single process parameter can be manipulated to vary particle size within uniformly sized droplets. The technique allows the polymerized particle size to be determined independently of droplet size, which surpasses previous reported microfluidic methods for hydrogel particle production, both synthetic [48,49] and natural [50], in simplicity, versatility, and throughput, due to its potential to control particle fabrication over a wide range of sizes at high production rates. While evidence of oxygen inhibition in PEGDA droplets photopolymerized within PDMS microfluidic devices has been present in reports by other groups [48,49,51], it has not been commented upon, nor has its potential to control particle size been suggested. Additionally, we have quantified the effect of different photopolymerization parameters, including the UV dose and macromer solution composition, on the unpolymerized shell thickness. This platform also allows the study of droplet photopolymerization kinetics by coupling empirical results with a reaction-diffusion model to quantify the sensitivity of each variable upon the photopolymerization of hydrogel particles within microfluidic emulsion droplets.

Kinetic models for the photopolymerization of multifunctional acrylates have been previously developed to accurately describe the effect of oxygen inhibition on polymer coatings, membranes [52,53], and thin films [54]. These models have been adapted to microfluidic contexts to describe and predict the size of a particle produced via stop flow lithography in microfluidic devices under different exposure conditions [45] and to explain the presence of an unpolymerized shell around a hydrogel particle when photopolymerizing droplets in ambient conditions [47]. There remains a need for a quantitatively predictive model to accurately describe the sensitivity of hydrogel particle size to changing droplet composition or exposure conditions. By understanding the influence of each parameter in the hydrogel photopolymerization process, we can exploit oxygen inhibition to produce particles that are <10 μm or even submicron from larger, easily produced droplet templates.

Here, we perform a systematic characterization of the effects of hydrogel-forming parameters on oxygen-inhibited PEGDA photopolymerization within emulsion droplets. The presented reaction-diffusion model accurately captures stoichiometric and photochemical effects on polymerization rate, and incorporates a previously unappreciated relationship between solution viscosity and oxygen diffusivity. Having produced a reaction-diffusion model that completely describes the full range of empirical results